National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
Division of Microbiology and Infectious Diseases (DMID)

POLICY AND GUIDELINES FOR DATA AND SAFETY MONITORING

I. Introduction

The Division of Microbiology and Infectious Diseases (DMID) supports, through both the contract and grant mechanism, a large number of clinical studies and trials. All DMID studies are conducted in accordance with DHHS regulations 45 CFR 46, which provide for the protection of study participants. To assure that procedures are in place to protect the safety of participants while assuring the validity and integrity of the study, DMID has adopted policies which mandate that a safety monitoring plan be established for all clinical trials. This requirement pertains to all studies that evaluate investigational test articles, studies in which there is a potential for harm to participants, and other studies in which independent assessments are required to assure objectivity. These policies apply to all DMID-sponsored research, regardless of funding mechanism, and are consistent with the NIH Policy for Data and Safety Monitoring issued on June 10, 1998 (http://grants.nih.gov/grants/guide/notice-files/not98-084.html) and Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials issued on June 5, 2000 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html). The NIH policy requires that each Institute and Center (IC) have a system for the appropriate oversight and monitoring of the conduct of clinical trials that ensures the safety of participants and the validity and integrity of the data. The policy further elaborates that monitoring should be commensurate with risks and with the size and complexity of the trials. Generally, the NIH requires Data and Safety Monitoring Boards (DSMBs) for Phase III clinical trials. For earlier trials (Phase I and II), a DSMB may be appropriate if the studies have multiple clinical sites, are blinded (masked), or employ particularly high-risk interventions or vulnerable populations. For other Phase I and Phase II trials, alternative formats may be utilized for monitoring.

This document provides further guidance for monitoring of all clinical trials supported by DMID. In addition to the general guidelines, specific guidelines for each of three different formats for independent monitoring that are described in section III below are attached.

II. Purpose

The purpose of data and safety monitoring is to provide an independent and objective review of interim safety and, if appropriate, efficacy data. In addition, data and safety monitoring can provide independent and objective review of the overall conduct of the study in order to protect the safety of volunteers and to ensure the integrity of the data. Monitoring bodies are advisory to DMID and their recommendations, while given careful consideration, are not binding. The primary charge to the advisory members is to monitor safety, study conduct, and study progress as well as accumulated data. They also provide advice to DMID and the study investigators as to the appropriateness of continuing the study as designed. In certain situations, independent monitoring boards may also be asked to provide recommendations concerning, for example, the need for extended follow-up or for initiation of related studies based on their findings.

All clinical research that entails greater than "minimal risk" requires independent monitoring. "Minimal risk" is defined in 45 CFR 46, Section 102 (i) as: *a risk where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological*

examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than doing so as part of a routine physical examination.

III. Formats for Monitoring

Three standard formats are available for independent monitoring of DMID-sponsored studies: 1) Data and Safety Monitoring Board (DSMB), 2) Safety Monitoring Committee (SMC), and 3) Independent Safety Monitor (ISM). Each is briefly summarized below. Detailed guidelines for the establishment and functioning of each are provided in Attachments I, II, and III, respectively. The DMID Program or Project Officer (PO refers to either) who has lead programmatic responsibility for a study, in consultation with the Chief, Office of Clinical Research Affairs (OCRA), determines which of these types of monitoring is appropriate based on the particular study design, study population, research environment, and degree of risk anticipated.

1. Data and Safety Monitoring Board. A DSMB is an independent group of experts that advises DMID and the study investigators. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to DMID concerning the continuation, modification, or termination of the trial. DSMBs meet regularly and whenever any special need arises to review study conduct and cumulative study data, and to recommend whether the study should continue without change, be modified, or be terminated. Recommendations to modify, suspend or terminate a trial may be based on any aspects of the trial it considers. A DSMB member's recommendation to terminate a trial based on finding efficacy (i.e., early rejection of the null hypothesis concerning the primary endpoint) requires statistical adjustments for interim evaluations and thus requires a pre-specified plan for interim statistical analysis. Therefore, it is essential that the DSMB for such trials include a member with appropriate statistical expertise. All DMID-sponsored Phase III trials are subject to DSMB review. DSMB oversight should be considered for other clinical trials, such as masked (blinded) Phase I and Phase II trials and for some unmasked Phase II trials.

2. Safety Monitoring Committee (SMC)

   The Safety Monitoring Committee (SMC) is an independent group of experts that advises DMID and the study investigators for many Phase I and smaller Phase II trials. ***The primary responsibility of the SMC is to monitor participant safety.*** Roles and responsibilities are similar to those of a DSMB except interim evaluations of efficacy are not performed. Investigators and POs should consider having at least one member of the SMC serve as an Independent Safety Monitor (see below). The SMC must be able to convene on an *ad hoc* basis when immediate safety concerns arise. Its members may be from the investigator's institution or other participating sites but should not be directly involved with the trial or under the investigator's supervision. It may be sufficient for a SMC to rely on an *ad hoc* or study statistician to assist in interpreting the results, thereby obviating the need to have a statistician as a member.

3. Independent Safety Monitor (ISM)

The Independent Safety Monitor (ISM) is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur, with follow-up through

resolution. The ISM evaluates individual and cumulative participant data when making recommendations regarding safe continuation of the study.

An ISM could be the sole monitor for the study or may perform this role as a member of a DSMB or SMC. An ISM is appropriate as the sole independent safety monitor for small, early phase studies considered to be low risk, such as some pharmacokinetics or immunogenicity studies, or other studies of short duration. DSMBs and SMCs should consider the need to designate one or more members as ISM(s). In the case of DSMBs, the ISM focus may be directed at serious adverse events rather than all adverse events.

IV. Relationship Between Safety Monitoring Groups and Institutional Review Boards (IRB)

Once a safety monitoring group is established, each of the relevant Institutional Review Boards (IRBs) should be informed of the operating procedures with regard to data and safety monitoring (e.g., who, what, when, and how monitoring will take place). This information will serve to assure the IRB that the safety of the research participants is appropriately monitored. If the IRB is not satisfied with the monitoring procedures, it should request modifications. While it is recognized that it may not be possible to satisfy every IRB completely, IRB comments should be considered seriously.

Implementation procedures are provided in the NIH policy on "Guidance on Reporting Adverse Events to IRBs for NIH-supported Multicenter Clinical Trials" dated June 11, 1999 (http://grants.nih.gov/grants/guide/notice-files/not99-107.html). While this policy applies specifically to DSMBs, applicability should be considered for all monitoring formats.

V. International Clinical Trials

General principles for data and safety monitoring apply to all international studies. Procedures may need to be modified to accommodate the policies, regulations, and cultural preferences of the host country.